Kongeriget Danmark

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Patent- og Varemærkestyrelsen
Kongeriget Danmark

Patent- og Varemærkestyrelsen
Erhvervsministeriet

TAASTRUP 14 June 2001

Karin Schlichting
Head Clerk

Novel Process

The present invention relates to novel processes for preparing pharmaceutically active compounds and intermediates therefor.

Pharmaceutical active compounds acting as potent and selective potassium channel openers that, by inhibiting insulin release and inducing β-cell rest, can be used in treatment of Type I and Type II diabetes are described in PCT Publication WO 97/26265. The compounds listed on page 46, line 33 to page 47, line 15 in PCT Publication WO 97/26265 are preferred.

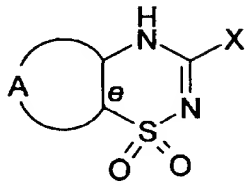
Ways of synthesising those compounds are described in PCT Publication WO 97/26265 on pages 20 to 25 and in PCT Publication WO 99/03861 .

The present invention provides alternative methods of synthesis for the above mentioned compounds in a more efficient way.

USP 5,459,138 discloses certain pyridothiadiazines and their preparation. However, the patent relates to the synthesis of pyridines only and contains no disclosure as regards the synthesis of the less reactive 5 membered heterocyclic ring systems.

The present invention has been developed on the basis that compounds of formula I below are either valuable chemical intermediates useful for the manufacture of pharmaceutical active compounds, such as those compounds listed on page 46 , line 33 to page 47, line 15 in PCT Publication WO 97/26265, or are themselves active compounds, such as disclosed in PCT Publication WO 97/26265.

The present invention provides novel processes for the preparation of fused 1,2,4-thiadiazine derivatives of the general formula I:



(I)

wherein X is NR^2R^3, SR^1, $S(=O)R^1$, $S(=O)_2R^1$, or OR^1, wherein R^1 is hydrogen, C_{3-6}-cycloalkyl or (C_{3-6}-cycloalkyl)C_{1-6}-alkyl the C_{3-6}-cycloalkyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms, optionally being mono- or polysubstituted with halogen, cyano, trifluoromethyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, aryl, arylalkyl, hydroxy, oxo, nitro, amino, C_{1-6}-monoalkyl or dialkylamino; or straight or branched C_{1-18}-alkyl, C_{2-18}-alkenyl or C_{2-18}-alkynyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{3-6}-cycloalkyl, nitro, amino, C_{1-6}- monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C_{1-6}-alkoxycarbonyl, carbamoyl, formylamino, C_{1-6}-alkylcarbonylamino, aryl, aryloxy, arylalkoxy; bicycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, aryloxy, arylalkoxy, nitro, amino, C_{1-6}-monoalkyl- or dialkylamino, cyano, oxo, acyl or C_{1-6}-alkoxycarbonyl;

R^2 is hydrogen; hydroxy; C_{1-6}-alkoxy; or C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{2-6}- alkenyl or C_{2-6}-alkynyl optionally mono- or polysubstituted with halogen;

R^3 is hydrogen, C_{3-6}-cycloalkyl or (C_{3-6}-cycloalkyl)C_{1-6}-alkyl, the C_{3-6}-cycloalkyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms; or straight or branched C_{1-18}-alkyl optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{3-6}-cycloalkyl, aryl, aryloxy, arylalkoxy, nitro, amino, C_{1-6}-monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C_{1-6}-alkoxycarbonyl, or carbamoyl;

or R^3 is $-OR^4$; $-C(=Z)R^4$; $-NR^4R^5$; bicycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, aryloxy,

arylalkoxy, nitro, amino, C_{1-6}-monoalkyl- or dialkylamino, cyano, oxo, acyl or C_{1-6}-alkoxycarbonyl;

wherein R^4 is hydrogen; C_{3-6}-cycloalkyl or (C_{3-6}-cycloalkyl)C_{1-6}-alkyl, the C_{3-6}-cycloalkyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms; or straight or branched C_{1-18}-alkyl optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{3-6}-cycloalkyl, aryl, aryloxy, arylalkoxy, nitro, amino, C_{1-6}-monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C_{1-6}-alkoxycarbonyl, or carbamoyl;

Z is O or S;

R^5 is hydrogen; C_{1-6}-alkyl; C_{2-6}-alkenyl; C_{3-6}-cycloalkyl optionally mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy;
or, when or R^3 is $-NR^4R^5$, R^4 and R^5 together with the nitrogen atom form a 3-12 membered mono- or bicyclic system, in which one or more of the carbon atoms may be exchanged with nitrogen, oxygen or sulfur, each of these ring systems optionally being mono- or polysubstituted with halogen, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, nitro, amino, cyano, trifluoromethyl, C_{1-6}-monoalkyl- or dialkylamino, oxo;

or, when X is NR^2R^3, R^2 and R^3 together with the nitrogen atom form a 3-12 membered mono- or bicyclic system, in which one or more of the carbon atoms may be exchanged with nitrogen, oxygen or sulfur, each of these ring systems optionally being mono- or polysubstituted with halogen, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, nitro, amino, cyano, trifluoromethyl, C_{1-6}-monoalkyl- or dialkylamino or oxo;

A together with the carbon atoms forming bond *e* of formula I represents a 5 membered heterocyclic system comprising one or more nitrogen-, oxygen- or sulfur atoms, the heterocyclic systems optionally being mono- or polysubstituted with halogen; C_{1-18}-alkyl; C_{3-6}-cycloalkyl; hydroxy; C_{1-6}-alkoxy; C_{1-6}-alkoxy-C_{1-6}-alkyl; nitro; amino; cyano; cyanomethyl; perhalomethyl; C_{1-6}-monoalkyl- or dialkylamino; sulfamoyl; C_{1-6}-alkylthio; C_{1-6}-alkylsulfonyl; C_{1-6}-alkylsulfinyl; C_{1-6}-alkylcarbonylamino; arylthio, arylsulfinyl, arylsulfonyl, aryl, arylalkyl, aryloxy, the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, perhalomethyl, halogen, hydroxy or C_{1-6}-alkoxy; C_{1-6}-alkoxycarbonyl; C_{1-6}-alkoxycarbonyl-C_{1-}

$_{6}$-alkyl; carbamyl; carbamylmethyl; C_{1-6}-monoalkyl- or dialkylaminocarbonyl; C_{1-6}-monoalkyl- or dialkylaminothiocarbonyl; ureido; C_{1-6}-monoalkyl- or dialkylaminocarbonylamino, thiocarbamyl; thioureido; C_{1-6}-monoalkyl- or dialkylaminothiocarbonyl- amino; C_{1-6}-monoalkyl- or dialkylaminosulfonyl; carboxy; carboxy-C_{1-6}-alkyl; acyl; formyl; or a 5 - 6 membered nitrogen, oxygen or sulfur containing ring, optionally substituted with C_{1-6}-alkyl or phenyl, the phenyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, perhalomethyl, halogen, hydroxy or C_{1-6}-alkoxy;

or a salt thereof with a pharmaceutically acceptable acid or base.

Within its scope the invention the process for preparation of compounds of formula I includes all optical isomers of compounds of formula I, some of which are optically active, and also their mixtures including racemic mixture thereof.

The scope of the invention also includes all tautomeric forms of the compounds of formula I as well as metabolites or prodrugs of a compound of formula I.

The salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts or optionally alkylated ammonium salts, such as hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, trifluoroacetic, trichloroacetic, oxalic, maleic, pyruvic, malonic, succinic, citric, tartaric, fumaric, mandelic, benzoic, cinnamic, methanesulfonic, ethanesulfonic, picric and the like, and include acids related to the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) and incorporated herein by reference, or lithium, sodium, potassium, magnesium and the like.

A "metabolite" of a compound disclosed in this application is an active derivative of a compound disclosed herein which is produced when the compound is metabolized. Metabolites of compounds disclosed herein can be identified either by administration of a compound to a host and an analysis of blood samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the incubant. A "prodrug" is a compound that either is converted into a compound disclosed in the application in vivo or has the same active metabolite as a compound disclosed in this application.

The term "C_{1-6}-alkoxy" as used herein, alone or in combination, refers to a straight or

branched monovalent substituent comprising a C_{1-6}-alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen and having 1 to 6 carbon atoms e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy.

The terms "C_{2-6}-alkenyl" and "C_{2-18}-alkenyl" as used herein refers to an unsaturated hydrocarbon chain having 2-6 or 2-18 carbon atoms and one double bond such as e.g. vinyl, 1-propenyl, allyl, isopropenyl, n-butenyl, n-pentenyl and n-hexenyl.

The term "C_{3-6}-cycloalkyl" as used herein refers to a radical of a saturated cyclic hydrocarbon with the indicated number of carbons such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

The terms "C_{2-6}-alkynyl" and "C_{2-18}-alkynyl" as used herein refers to unsaturated hydrocarbons which contain triple bonds, such as e.g. -C≡CH, -C≡CCH_3, -CH_2C≡CH, -CH_2CH_2C≡CH, -CH(CH_3)C≡CH, and the like.

The term "C_{1-6}-alkoxy-C_{1-6}-alkyl" as used herein refers to a group of 2-12 carbon atoms interrupted by an O such as e.g. CH_2-O-CH_3, CH_2-O-CH_2-CH_3, CH_2-O-CH(CH_3)$_2$ and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "perhalomethyl" means trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl.

The terms "C_{1-6}-alkyl", "C_{1-12}-alkyl" and "C_{1-18}-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms such as e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 4-methylpentyl, neopentyl, n-hexyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1,2,2-trimethylpropyl and the like. The term "C_{1-18}-alkyl" as used herein also includes secondary C_{3-6}-alkyl and tertiary C_{4-6}-alkyl.

The term "C_{1-6}-monoalkylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms such as e.g. methylamino, ethylamino, propylamino, n-butylamino, sec-butylamino, isobutylamino, tert-butylamino, n-pentylamino,

2-methylbutylamino, n-hexylamino, 4-methylpentylamino, neopentylamino, n-hexylamino, 2,2-dimethylpropylamino and the lik .

The term "C_{1-6}-dialkylamino" as used herein refers to an amino group wherein the two hydrogen atoms independently are substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms; such as dimethylamino, N-ethyl-N-methylamino, diethylamino, dipropylamino, N-(n-butyl)-N-methylamino, di(n-pentyl)amino, and the like.

The term "acyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-alkyl group linked through a carbonyl group; such as e.g. acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl, and the like.

The term "C_{1-6}-alkoxycarbonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-alkoxy group linked through a carbonyl group; such as e.g. methoxycarbonyl, carbethoxy, propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 3-methylbutoxycarbonyl, n-hexoxycarbonyl and the like.

The term "3-12 membered mono- or bicyclic system" as used herein refers to a monovalent substituent of formula $-NR^2R^3$ or $-NR^8R^9$ where R^2 and R^3, or R^8 and R^9 together with the nitrogen atom form a 3-12 membered mono- or bicyclic system, in which one or more of the carbon atoms may be exchanged with nitrogen, oxygen or sulfur, such as 1-pyrrolidyl, piperidino, morpholino, thiomorpholino, 4-methylpiperazin-1-yl, 7-azabicyclo[2.2.1]heptan-7-yl, tropanyl and the like.

The term "3-6 membered saturated ring system" as used herein refers to a monovalent substituent comprising a monocyclic saturated system containing one or more hetero atoms selected from nitrogen, oxygen and sulfur and having 3-6 members and having its free valence from a carbon atom, e.g. 2-pyrrolidyl, 4-piperidyl, 3-morpholinyl, 1,4-dioxan-2-yl, 5-oxazolidinyl, 4-isoxazolidinyl, or 2-thiomorpholinyl.

The term "bicycloalkyl" as used herein refers to a monovalent substituent comprising a bicyclic structure made of 6-12 carbon atoms such as e.g. 2-norbornyl, 7-norbornyl, 2-bicyclo[2.2.2]octyl, and 9-bicyclo[3.3.1]nonanyl.

The term "aryl" as used herein refers to phenyl, 1-naphthyl, or 2-naphthyl.

The term "heteroaryl" as used herein, alone or in combination, refers to a monovalent substituent comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine, and purine.

The term "arylalkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphtylmethyl, 2-(1-naphtyl)ethyl and the like.

The term "aryloxy" as used herein refers to phenoxy, 1-naphthyloxy or 2-naphthyloxy.

The term "arylalkoxy" as used herein refers to a C_{1-6}-alkoxy group substituted with an aromatic carbohydride, such as benzyloxy, phenethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-(1-naphtyl)ethoxy and the like.

The term "C_{1-6}-alkylsulfonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-alkyl group linked through a sulfonyl group such as e.g. methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, n-pentylsulfonyl, 2-methylbutylsulfonyl, 3-methylbutylsulfonyl, n-hexylsulfonyl, 4-methylpentylsulfonyl, neopentylsulfonyl, n-hexylsulfonyl and 2,2-dimethylpropylsulfonyl.

The term "C_{1-6}-monoalkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-monoalkylamino group linked through a sulfonyl group such as e.g. methylaminosulfonyl, ethylaminosulfonyl, n-propylaminosulfonyl, isopropylaminosulfonyl, n-butylaminosulfonyl, sec-butylaminosulfonyl, isobutylaminosulfonyl, tert-butylaminosulfonyl, n-pentylaminosulfonyl, 2-methylbutylaminosulfonyl, 3-methylbutylaminosulfonyl, n-hexylaminosulfonyl, 4-methylpentylaminosulfonyl, neopentylaminosulfonyl, n-hexylaminosulfonyl and 2,2-dimethylpropylaminosulfonyl.

The term "C_{1-6}-dialkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-dialkylamino group linked through a sulfonyl group such as

dimethylaminosulfonyl, N-ethyl-N-methylaminosulfonyl, diethylaminosulfonyl, dipropylaminosulfonyl, N-(n-butyl)-N-methylaminosulfonyl, di(n-pentyl)aminosulfonyl, and the like.

The term "C_{1-6}-alkylsulfinyl" as used herein refers to a monovalent substituent comprising a straight or branched C_{1-6}-alkyl group linked through a sulfinyl group (-S(=O)-); such as e.g. methylsulfinyl, ethylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl, and the like.

The term "C_{1-6}-alkylcarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with an acyl group, such as e.g. acetamido, propionamido, isopropylcarbonylamino, and the like.

The term "(C_{3-6}-cycloalkyl)C_{1-6}-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1 to 6 carbon atoms and being monosubstituted with a C_{3-6}-cycloalkyl group, the cycloalkyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; such as e.g. cyclopropylmethyl, (1-methylcyclopropyl)methyl, 1-(cyclopropyl)ethyl, cyclopentylmethyl, cyclohexylmethyl, and the like.

The term "C_{1-6}-alkylthio" or "C_{1-6}-alkylsulfanyl" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a lower alkyl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom and having 1 to 6 carbon atoms e.g. methylsulfanyl, ethylsulfanyl, propylsulfanyl, butylsulfanyl, pentylsulfanyl.

The term "arylthio" or "arylsulfanyl" as used herein, alone or in combination, refers to an aryl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom, the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; e.g. phenylsulfanyl, (4-methylphenyl)sulfanyl, (2-chlorophenyl)sulfanyl, and the like.

The term "arylsulfinyl" as used herein refers to an aryl group linked through a sulfinyl group (-S(=O)-), the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; such as e.g. phenylsulfinyl, (4-chlorophenyl)sulfinyl, and the like.

The term "arylsulfonyl" as used herein refers to an aryl group linked through a sulfonyl group,

the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; such as e.g. phenylsulfonyl, tosyl, and the like.

The term "C_{1-6}-monoalkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-monoalkylamino group linked through a carbonyl group such as e.g. methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, n-butylaminocarbonyl, sec-butylaminocarbonyl, isobutylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, 2-methylbutylaminocarbonyl, 3-methylbutylamino-carbonyl, n-hexylaminocarbonyl, 4-methylpentylaminocarbonyl, neopentylaminocarbonyl, n-hexylaminocarbonyl and 2-2-dimethylpropylaminocarbonyl.

The term "C_{1-6}-dialkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-dialkylamino group linked through a carbonyl group such as dimethylaminocarbonyl, N-ethyl-N-methylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, N-(n-butyl)-N-methylaminocarbonyl, di(n-pentyl)aminocarbonyl, and the like.

The term "C_{1-6}-monoalkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C_{1-6}-monoalkylaminocarbonyl group, e.g. methylaminocarbonylamino, ethylaminocarbonylamino, n-propylaminocarbonylamino, isopropylaminocarbonylamino, n-butylaminocarbonylamino, sec-butylaminocarbonylamino, isobutylaminocarbonylamino, tert-butylaminocarbonylamino, and 2-methylbutylaminocarbonylamino.

The term "C_{1-6}-dialkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C_{1-6}-dialkylaminocarbonyl group, such as dimethylaminocarbonylamino, N-ethyl-N-methylaminocarbonylamino, diethylaminocarbonylamino, dipropylaminocarbonylamino, N-(n-butyl)-N-methylaminocarbonylamino, di(n-pentyl)aminocarbonylamino, and the like.

The term "5-membered heterocyclic system" as used herein refers to: a monocyclic unsaturated or saturated system containing one, two or three hetero atoms selected from nitrogen, oxygen and sulfur and having 5 members, e.g. pyrrole, furan, thiophene, pyrroline, dihydrofuran, dihydrothiophene, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, thiazole, isoxazole, isothiazole, 1,2,3-oxadiazole, furazan, 1,2,3-triazole, 1,2,3-thiadiazole or

2,1,3-thiadiazole.

The term "5- or 6-membered nitrogen, oxygen or sulfur containing ring" as used herein refers to a monovalent substituent comprising a monocyclic unsaturated or saturated system containing one or more nitrogen, oxygen or sulfur atoms and having 5 or 6 members, e.g. pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholino, thiomorpholino, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl, and 1,4-dioxolanyl.

According to the invention, the term "base" as used herein refers to inorganic and organic bases which can be used to make a certain transformation taking place.
Useful bases are:
Hydroxides as *e.g.* sodium, lithium, magnesium, calcium, barium, potassium or caesium hydroxide .
Carbonates as *e.g.* sodium, lithium, magnesium, calcium, barium, potassium or caesium carbonate.
Alcoholates of sodium, lithium, magnesium, calcium, barium, potassium or caesium.
Alcoholates of t-butanol, methanol, ethanol, 1-propanol, 2-propanol.
Tertiary amines as *e.g.* dimethylaminopyridine, triethylamine.
Phosphates as *e.g.* sodium, lithium, magnesium, calcium, barium, potassium or caesium phosphate.
Sulphates as *e.g.* sodium, lithium, magnesium, calcium, barium, potassium or caesium sulphate.
Secondary amine bases as *e.g.* sodium, lithium, magnesium, calcium, barium, potassium or caesium bis(isopropyl)amide and bis(cyclohexyl)amides and *e.g.* sodium, magnesium, calcium, barium, potassium or caesium bis(trimetylsilyl)amide.
Hydrides as *e.g.* sodium hydride and potassium hydride
Carboxylic acid salts as e.g. sodium, lithium, magnesium, calcium, barium, potassium or caesium formate, acetate, propionate.

In a preferred embodiment the bases are selected from the following inorganic bases:
Hydroxides or carbonates of sodium, lithium, magnesium, calcium, barium, potassium or caesium.

According to the inv ntion, the term "solvent 1" as used herein refers to all solvents and combinations of solvents (e.g. mixtures of organic solvents or mixtures of one or more organic solvents and water) which can be used to make a certain transformation taking place selected from:
water, organic solvents as *e.g.* toluene, xylene, different ethers as *t*-butyl-methylether, hexane, heptane, *N,N*-dimethylformamide, *N*-methyl-2-pyrrolidinone, sulfolane, dimethylsulfoxide, 1,3-dimethyl-3,4,5,6-tetrahydroxy-2(1H)-pyrimidinone, chlorinated solvents, acetone and alkyl esters such as ethyl acetate and isopropyl acetate.

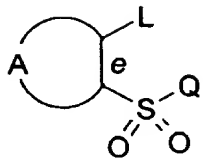
In a preferred embodiment "solvent 1" is a two phase system of water and an organic solvent selected from ether, toluene or *t*-butyl-methylether or a one phase system of water and acetone.

According to the invention, the term "solvent 2" as used herein refers to all solvents and combinations of solvents (e.g. mixtures of organic solvents or mixtures of one or more organic solvents and water) which can be used to make a certain transformation taking place selected from:
organic solvents such as toluene, xylene, *N,N*-dimethylformamide, *N*-methyl-2-pyrrolidinone, sulfolane, dimethylsulfoxide or 1,3-dimethyl-3,4,5,6-tetrahydroxy-2(1H)-pyrimidinone and alcohols such as ethanol, n-butanol, n-propanol, *iso*-propanol and water.

According to the invention, the term "metal catalyst" as used herein refers to all metal catalysts which are capable of making the transformation taking place at a low temperatures or similar mild conditions selected from:
Copper or a copper (I) or copper (II) salt such as copper oxide, copper chloride, copper bromide or copper iodide or a palladium catalyst such as $Pd(PPh_3)_4$, $Pd(dba)_2/2(o\text{-}tolyl)_3P$, $PdCl_2(DPPF)$, $PdCl_2(Ph_2P[CH_2]PPh_2)$ wherein "Ph" means "phenyl".

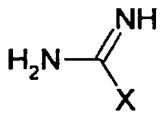
More particularly the present compounds of formula I are prepared by

a) reacting a compound of formula II



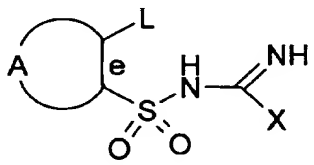
(II)

wherein A is as defined above, L is a leaving group selected from alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro or halogen and Q is halogen with a compound of formula III,



(III)

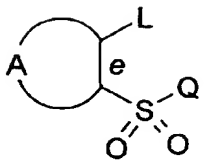
wherein X is NR^2R^3, wherein R^2 and R^3 are defined above, or a suitable salt thereof, in the presence of a suitable base in solvent 1 to form a compound of formula IV



(IV)

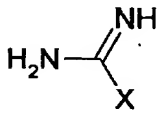
wherein A, L and X are as defined above, and thereupon cyclization of a compound of formula IV by treatment without or with a metal catalyst in solvent 2 in the presence of a base to form a compound of formula I, or

b) reacting a compound of formula II



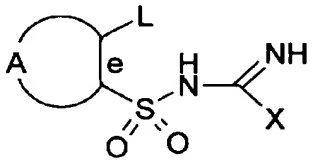
(II)

wherein A is as defined above, L is a leaving group selected from alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl or halogen and Q is halogen with a compound of formula III,



(III)

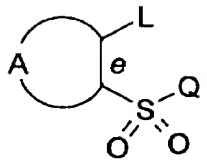
wherein X is SR^1, $S(=O)R^1$ or $S(=O)_2R^1$, wherein R^1 is defined above, or a suitable salt thereof, in the presence of a suitable base in solvent 1 to form a compound of formula IV



(IV)

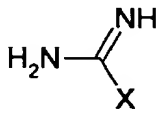
wherein A, L and X are as defined above, and thereupon cyclization of a compound of formula IV by treatment with or without a metal catalyst in solvent 2 in the presence of a base to form a compound of formula I, or

c) reacting a compound of formula II



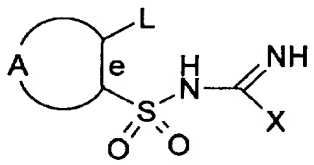
(II)

wherein A is as defined above, L is a leaving group selected from alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl or halogen and Q is halogen with a compound of formula III,



(III)

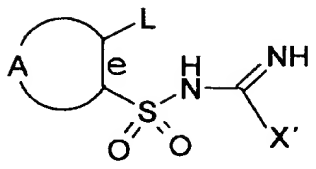
wherein X is OR^1, wherein R^1 is defined above, or a suitable salt thereof, in the presence of a suitable base in solvent 1 to form a compound of formula IV



(IV)

wherein A, L and X are as defined above, and thereupon cyclization of a compound of formula IV by treatment with or without a metal catalyst in solvent 2 in the presence of a base to form a compound of formula I, or

d) transforming a compound of formula IV to a compound of formula IV'



(IV')

wherein A and L are as defined above and X' is transformed into X and X' ≠ X, and cyclization of a compound of formula IV' by treatment with or without a metal catalyst in solvent 2 in the presence of a base to form a compound of formula I, or

e) transforming a compound of formula I, prepared as described above, by oxidation or substitution or both, to form another compound of formula I in analogy with known methods as described in WO97/26265.

Where intermediate compounds in the process of this invention are novel, such intermediates form another aspect of this invention.

Therapeutic uses of compounds selected from the group consisting of

3-Amino-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

7-Bromo-6-chloro-3-propylaminothieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

7-Bromo-3-(*sec*-butylamino)-6-chloro-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

7-Bromo-6-chloro-3-cyclobutylamino-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-methylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide or

6-Chloro-3-methylsulfinyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

obtained by a process of the present invention include treatment of and/or prevention of dyslipidemia, Type I diabetes, NIDDM, hypertriglyceridemia, syndrome X, insulin resistance, impaired glucose tolerance, obesity, diabetic dyslipidemia, hyperlipidemia and hypertension. More particular, the compounds are useful in the treatment of Type I and Type II diabetes. The compounds of the invention may also be useful for the treatment of eating disorders such as anorexia or bulimia by virtue of their appetite regulating properties.

Accordingly, the present invention also provides a pharmaceutical composition for treatment or prophylaxis of the disorder comprising one of the above mentioned compounds obtained using the process of the present invention and a pharmaceutically acceptable carrier, the use of one of the above mentioned compounds obtained using the process of the present

invention to manufacture a medicament in solid or liquid form for the treatment or prophylaxis of the disorders and a m thod of treating the disorders which comprises administering an effective or prophylactic amount of one of the above mentioned compounds obtained using the process of the present invention to a person suffering from one or more of the disorder's.

The present invention is illustrated by the following examples.

The abbreviation MTBE was used for methyl *tert*-butyl ether.

In the examples the following HPLC method was used:

HPLC method

Gradient HPLC assay:

Reagents:

- Acetonitrile
- Trifluoroacetic acid
- Millipore filtered water

HPLC Conditions:

- column: 250 x 4.0 mm, 5mm C-18 YMC-Silica 120 Å prepared at Novo Nordisk A/S
- Flow: 1.0 ml/min
- Oven temp.: 35°C
- Detector wavelength: 250 nm.
- Run time: 40 min.
- Gradient program:

Time Min.	Pump A Acetonitrile 0,1% TFA	Pump B Water 0,1% TFA	Flow ml/min
0,0	20	80	1,00
25,0	80	20	1,00

30,0	80	20	1,00
35,0	20	80	1,00
45,0	20	80	1,00

Preparation of solutions:

Acetonitrile containing 0.1% TFA:

Water containing 0.1% TFA:

Isocratic HPLC method

Reagents:

- Acetonitrile,
- Triethylamine
- Millipore filtered water
-

HPLC conditions:

- Column: 250 × 4.0 mm, 5mm C-18 YMC-Silica 120 Å
- Flow: 1.0 ml/min
- Detector wavelength: 250 nm.
- Run time: 30 min.

Preparation of HPLC eluent

50 % acetonitrile at pH 3:

Triethylamine (3.5 ml) was added to water (950 ml). The pH was adjusted to pH 3 with 10 % phosphoric acid followed by addition of water to totally 1 l. Acetonitrile (1 l) was added and the mixture filtered (0.45 µm).

The starting materials are either known compounds or compounds which may be prepared in analogy with the preparation of known compounds or in analogy with known methods.

EXAMPLE 1

7-Bromo-6-chloro-3-methylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

a) N-(2,5-Dichloro-4-bromo-3-thienylsulfonyl)-S-methylisothiourea

4-Bromo-2,5-dichloro-thiophene-3-sulfonyl chloride (5.95 g, 18.0 mmol) was gradually added to a stirred mixture of S-methylisothiourea sulfate (5.2 g, 18.6 mmol) in 38 ml of 1 N sodium hydroxide and 90 ml of ether. The mixture was stirred at room temperature for 20 h and the ether was evaporated in vacuo to give the product as an oil which solidified by stirring the aqueous phase. The precipitate was isolated by filtration and recrystallised from ethanol/water to give 4.95 g (72 %) of the title compound; mp 113-115°C ; ^{1}H-NMR (DMSO-d_6): δ 2.37(s, 3H), 8.28(br s, 1H), 8.97(br s, 1H); ^{13}C-NMR (DMSO-d_6): δ 14.8, 110.6, 125.1, 130.2, 136.8, 171.4.

b) 7-Bromo-6-chloro-3-methylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

Potassium carbonate (0.69 g, 5.0 mmol) was added to a solution of N-(2,5-dichloro-4-bromo-3-thienylsulfonyl)-S-methylisothiourea (1.92 g, 5.0 mmol) in 10 ml of dry *N,N*-dimethylformamide and the mixture was stirred at 120° C under nitrogen for 2 h and then concentrated to dryness. To the residue was added 5 ml of water and 4 M hydrochloric acid to pH < 2 and the resulting precipitate was isolated by filtration and washed with water to give 1.38 g (79 %) of the title compound; ^{1}H-NMR (CH_3OD): δ 2.59 (s, 3H); LC-MS: m/z 347/349/351 $(M+1)^+$.

EXAMPLE 2

7-Bromo-6-chloro-3-methylsulfinyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

To a suspension of 7-bromo-6-chloro-3-methylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide (695 mg, 2.0 mmol) in 50 ml of acetic acid was added 2 ml of 35% hydrogen peroxide . The mixture was stirred at room temperature for 20 h, and the white solid was isolated by filtration, washed with water and dried to give 460 mg (63 %) of the title compound; ^{1}H-NMR (DMSO-d_6): δ 2.85 (s, 3H).

EXAMPLE 3

7-Bromo-6-chloro-3-propylaminothieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

A solution of 7-bromo-6-chloro-3-methylsulfinyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide (100 mg, 0.275 mmol) in 0.5 ml of propylamine was stirred for 16 h at 65°C in a sealed glass screw cap vessel. The cooled solution was concentrated *in vacuo* and the residue was stirred with water (3 ml) followed by adjustment to pH < 2 with 4M hydrochloric acid. The product was isolated by filtration, washed with water and ether to give 90 mg (92 %) of the title compound; ^{1}H-NMR (DMSO-d_6): δ 0.89 (t, 3H), 1.52 (sext, 2H), 3.12 (q, 2H), 7.70 (br s, 1H), 11.50 (br s, 1H).

EXAMPLE 4

3-Amino-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

a) N-(3-Bromo-5-chloro-2-thienylsulfonyl)guanidine

3-Bromo-5-chloro-thiophene-2-sulfonyl chloride (0.5 g, 1.69 mmol) was added dropwise to a stirred mixture of guanidine carbonate (0.31 g, 1.72 mmol) in 3.4 ml of 1 N sodium hydroxide and 9 ml of ether. The mixture was stirred at room temperature for 18 h and then the white solid was isolated by filtration to give 435 mg (81 %) of the title compound; mp 236-238° C; ^{1}H-NMR (DMSO-d_6): δ 6.9 (br s, 4H), 7.37 (s, 1H).

b) 3-Amino-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

A mixture of N-(3-bromo-5-chloro-2-thienylsulfonyl)guanidine (319 mg, 1.0 mmol), potassium carbonate (140 mg, 1.0 mmol) and copper bronze (10 mg) in dry *N,N*-dimethylamide was stirred at 150° C for 90 min under nitrogen. To the cooled dark mixture was added 10 ml of water and the mixture was treated with decolorising charcoal and filtered. The filtrate was evaporated to dryness and the residue was treated with 10 ml of water and 4 M hydrochloric acid to pH < 2. The grey solid was isolated by filtration and recrystallised from ethanol to give 44 mg (18 %) of the title compound as white crystals; mp > 361° C; ^{1}H-NMR (DMSO-d_6): δ 7.02 (s, 1H), 7.10 (br s, 2H), 11.18 (s, 1H).

EXAMPLE 5

3-Butylamino-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

A solution of 3-amino-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide (50 mg, 0.21 mmol) in 0.5 ml of butylamine was stirred for 18 h at 120°C in a sealed glass screw cap vessel. The cooled solution was concentrated *in vacuo* and the residue was stirred with water (3 ml) followed by adjustment to pH < 2 with 4M hydrochloric acid. The product was isolated by filtration, washed with water and ether to give 35 mg (57 %) of the title compound; ^{1}H-NMR (DMSO-d_6): δ 0.89 (t, 3H), 1.2-1.6 (m, 4H), 3.19 (q, 2H), 7.05 (s, 1H), 7.31 (br s, 1H), 11.05 (br s, 1H).

EXAMPLE 6

7-Bromo-3-(*sec*-butylamino)-6-chloro-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

A solution of 7-bromo-6-chloro-3-methylsulfinyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide (200 mg, 0.55 mmol) in 1.0 ml of *sec*-butylamine was stirred for 18 h at 65°C in a sealed glass screw cap vessel. The cooled solution was stirred with water (4 ml) followed by adjustment to pH < 2 with 4M hydrochloric acid. The product was isolated by filtration and

washed with water to give 123 mg (60 %) of the title compound; ^{1}H-NMR (DMSO-d_6): δ 0.88 (t, 3H), 1.14 (d, 3H), 1.4-1.6 (m, 2H), 3.67 (br m, 1H), 7.55 (br s, 1H), 11.28 (br s, 1H).s, 1H).

EXAMPLE 7

7-Bromo-6-chloro-3-cyclobutylamino-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

A solution of 7-bromo-6-chloro-3-methylsulfinyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide (200 mg, 0.55 mmol) in 0.5 ml of cyclobutylamine was stirred for 18 h at 65°C in a sealed glass screw cap vessel. The cooled solution was stirred with water (4 ml) followed by adjustment to pH < 2 with 4M hydrochloric acid. The product was isolated by filtration, washed with water and recrystallised from methanol/water to give 72 mg (35 %) of the pure title compound; mp 341-42 °C dec.;^{1}H-NMR (DMSO-d_6): δ 1.55-1.78 (m, 2H), 1.87-2.12 (m, 2H), 2.14-2.34 (m, 2H), 4.12 (br sext, 1H), 8.02 (br d, 1H), 11.34 (br s, 1H).

EXAMPLE 8

6-Chloro-3-isopropylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

a) 3-Bromo-5-chlorothiophene-2-sulphonyl chloride

2-Chloro-4-bromothiophene (10 g) was added to chlorosulphonic acid (13.4 ml) at 0-5 °C under an atmosphere of nitrogen. After the addition, the reaction mixture was stirred at 0- 5 °C for about 30 min and then added to another flask containing water (20 ml), methyl-*tert*-butylether (MTBE) (30 ml) and heptane (30 ml) under stirring at 0 - 5 °C. The two phases were separated and the aqueous phase extracted with a mixture of heptane (25 ml) and MTBE (25 ml). The combined organic phases were dried with $MgSO_4$ and evaporated *in vacuo* to give the crude product as a purple oil (13.4 g). HPLC purity > 84% (isocratic HPLC method); ^{1}H-NMR ($CDCl_3$) δ: 7.09 (s, 1H). The crude product was used without further purification.

b) *N*-(3-Bromo-5-chlorothienylsulphonyl)-*N'*-isopropylurea

Isopropylguanidine hydrochloride (4.65 g), 2N sodium hydroxide (50 ml) and MTBE (250 ml) was stirred until all isopropylguanidine hydrochloride was dissolved. Crude 3-bromo-5-chlorothiophene-2-sulphonyl chloride (10 g) dissolved in MTBE (25 ml) was added drop by drop during 20 minutes at room temperature. The reaction mixture was stirred for 2 h until no starting material could be detected. The two phases were separated and the organic phase was extracted with ethyl acetate (50 ml × 3). The combined organic phases were dried with $MgSO_4$ and some of the solvent evaporated *in vacuo* to a volume of 10-70 ml. The formed crystals were separated to give 6.4 g of the title product. The mother liquor was evaporated *in vacuo* to give 5 g of an oil which contained some title product (Found: C, 26.85; H, 3.1; N 11.6. Calc. for $C_8H_{11}N_2O_2S_2BrCl$: C, 26.6; H, 3.1; N, 11.65); ^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 6H), 3.58-4.00 (m, 1H), 6.59 (bs, 1H), 7.03 (bs, 1H), 7.38 (s, 1H), 7.15-7.50 (bs, 1H).

c) 6-Chloro-3-isopropylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

A mixture of *N*-(3-Bromo-5-chlorothienylsulphonyl)-*N*-isopropylurea (2 g), copper (0.05 g), potassium carbonate (2 g), and a crystal of iodine was stirred in dry *N,N*-dimethylformamide (0.04 l) in a sealed glass screw cap vessel at 125 °C for 20 h. The reaction mixture was filtered and the filter cake washed with dimethylformamide (10 ml ×2). The pooled organic phases were evaporated to dryness, water (0.08 l) was added and the suspension filtered. The pH of the aqueous phase was adjusted to 1-2 with 2 N hydrochloric acid and the precipitated crude product was filtered off, washed with water (10 ml) and dried *in vacuo* (1.1 g, 72%).

EXAMPLE 9

6-Chloro-3-isopropylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

The same procedure as described in example 8c was used (*N*-(3-bromo-5-chlorothienylsulphonyl)-*N*-isopropylurea (0.2 g), Cu (10 mg), I_2 (one crystal)) together with procedures where copper and iodine (Cu, I_2) were substituted with copper(I) oxide (CuO) (22.9 mg), copper(I) chloride (CuCl) (15.8 mg), copper(I) bromide (CuBr) (23 mg), copper(I)

iodide (CuI) (30.5 mg) and omitted . After 1 h. the following results were obtained: Cu, I_2: 96% product; CuO: 96%; CuCl: 98%, CuBr: 92%; CuI: 94%; no Cu: <1%. After 3 h. the following results were obtained: Cu, I_2: 99% product; CuO: 99%; CuCl: 100%, CuBr: 100%; CuI: 100%; no Cu: 1%. After 18 h.: no Cu: 10%. The analytical results were obtained by using the described gradient HPLC assay. The figures are calculated as the ratio between product and starting material.

EXAMPLE 10

6-Chloro-3-isopropylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

A mixture of *N*-(3-Bromo-5-chlorothienylsulphonyl)-*N*-isopropylurea (200 mg), copper(I) oxide (23 mg), and potassium hydroxide (160 mg) was stirred in dry *N,N*-dimethylformamide (5 ml) in a sealed glass screw cap vessel at 120 °C. After 3 hours the amount of product formed was 94%. After 6 hours the amount of product was 97% (The data are found as described in example 9).

EXAMPLE 11

6-Chloro-3-isopropylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

N-(3-Bromo-5-chlorothienylsulphonyl)-*N*-isopropylurea (200 mg) was added to a glass screw cap vessel together with copper(I) oxide (2 mg), potassium carbonate (200 mg) and dry *N,N*-dimethylformamide (5 ml), sealed and heated to 120 °C. After 3 hours the amount of product formed was 85%. After 6 hours the amount of product was 98% (The data are found as described in example 9).

EXAMPLE 12

6-Chloro-3-isopropylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

N-(3-Bromo-5-chlorothienylsulphonyl)-*N*-isopropylurea (200 mg) was added to a glass screw cap vessel together with copper(I) oxide (23 mg), potassium carbonate (200 mg) and the following solvents: *N*-methyl-2-pyrolidone (NMP) (5 ml), sulpholane (5 ml), dimethylsulfoxide (DMSO) (5 ml), 1,3-dimethyl-3,4,5,6-tetrahydroxy-2(1H)-pyrimidinone (DMPU) (5 ml). After 1 hours the amount of product formed was NMP: 84%, Sulfolane: 45%, DMSO: 78%, DMPU 67% After 3 hours the amount of product formed was NMP: 100%, Sulfolane: 92%, DMSO: 100%, DMPU 100% (The data are found as described in example 9).

EXAMPLE 13

6-Chloro-3-isopropylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

N-(3-Bromo-5-chlorothienylsulphonyl)-*N*-isopropylurea (200 mg) was added to a glass screw cap vessel together with copper(I) oxide (2 mg), potassium hydroxide (160 mg) and dry toluene (10 ml), sealed and heated to 120 °C. After 6 hours the amount of product formed was 98% (The data are found as described in example 9).

EXAMPLE 14

3-Benzylsulfanyl-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

a) *N*-(3-Bromo-5-chlorothienylsulphonyl)-*S*-benzylisothiourea

S-Benzyl-thiuronium chloride (8.1 g), sodium hydroxide (2.2 g) and acetone (100 ml) was stirred for 5 minutes before crude 3-bromo-5-chlorothiophene-2-sulphonyl chloride (10 g) was added dropwise during 20 minutes at room temperature. The reaction mixture was stirred for 24 h. The suspension was evaporated *in vacuo* and the crude reaction mixture partitioned between 1N hydrochloric acid (30 ml) and dichloromethane (50 ml). The two phases were separated and the aqueous phase extracted with dichloromethane (50 ml × 4). The combined organic phases were dried with $MgSO_4$ and evaporated *in vacuo* to give the crude product (12.8 g). The crude product was suspended in toluene and the crystals

isolated by filtration (4.0 g); ^{1}H-NMR ($CDCl_3$) δ: 4.23 (s, 2H), 7.15-7.35 (m, 5H), 7.44 (s, 1H), 8.0-8.5 (bs, 1H), 8.8-9.4 (bs, 1H); ^{13}C-NMR ($CDCl_3$) δ: 33.1, 114.8, 125.6, 126.5, 127.1, 134.2, 135.0, 137.1, 157.1.

b) 3-Benzylsulfanyl-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

N-(3-Bromo-5-chlorothienylsulphonyl)-*S*-benzylisothiourea (2 g) was added to a glass screw cap vessel together with copper (0.05 g), potassium carbonate (2 g), iodine (a crystal) and dry *N,N*-dimethylformamide (0.03 l), sealed and heated to 125 °C for 1½ h. The reaction mixture was filtered and the filter cake washed with *N,N*-dimethylformamide (10 ml ×2). The pooled organic phases were evaporated to dryness, water (0.1 l) was added and the suspension filtered. The pH of the aqueous phase was adjusted to 1-2 with 2 N hydrochloric acid and the precipitated crude product was filtered off, washed with water (10 ml) and dried *in vacuo* (65 mg); $HPLC_{purity}$ (isocratic method): 96%; ^{1}H-NMR ($CDCl_3$) δ: 4.42 (s, 2H), 7.02 (s, 1H)7.15-7.76 (m, 5H).

EXAMPLE 15

6-Chloro-3-methylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

a) *N*-(3-Bromo-5-chlorothienylsulphonyl)-*S*-methylisothiourea

S-methyl-thiuronium sulphate (9.4 g), 2N sodium hydroxide (34 ml) and diethylether (180 ml) was stirred for 5 minutes. Crude 3-bromo-5-chlorothiophene-2-sulphonyl chloride (10 g) dissolved in diethylether (20 ml) was added dropwise during ½ h. under vigorously stirring at room temperature. The reaction mixture was stirred for 24 h. and the two phases were separated. The organic phase was extracted with water (50 ml × 3), dried with $MgSO_4$ filtered and evaporated *in vacuo* (10.1 g). A crystallisation of the crude product from a mixture of acetone and water provided the title product (8 g); ^{1}H-NMR ($CDCl_3$) δ: 2.45 (s, 3H), 6.93 (s, 1H), 5.5-6.8 (bs, 1H), 7.4-8.5 (bs, 1H); ^{13}C-NMR ($CDCl_3$) δ: 14.7, 112.0, 133.0, 134.1, 138.6, 171.3.

b) 6-Chloro-3-methylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

N-(3-Bromo-5-chlorothienosulphonyl)-*S*-methylthiourea (2 g) was add d to a glass screw cap vessel together with copper (0.06 g), potassium carbonate (2 g), iodine (a crystal) and dry *N,N*-dimethylformamid (0.04 l), sealed and heated to 120 °C for 3 h. The reaction mixture was filtered and the filter cake washed with *N,N*-dimethylformamide (10 ml × 2). The pooled organic phases were evaporated to dryness, water (0.1 l) was added and the pH was adjusted to 1-2 with 2 N hydrochloric acid. The suspension was filtered and the crude product washed with dichloromethane (10 ml) and dried *in vacuo* (0.2 g); ^{1}H-NMR (DMSO-d_6) δ: 2.50 (s, 3H), 7.00 (s, 1H) 12.8-13.5 (bs, 1H); ^{1}H-NMR (MeOD-d_4) δ: 2.59 (s, 3H), 6.84 (s, 1H); ^{13}C-NMR (NMR (MeOD-d_4) δ: 14.3, 118.5, 126.3, 136.2, 139.8, 160.4.

EXAMPLE 16

6-Bromo-3-isopropylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

a) N-(3,5-Dibromo-2-thienosulfonyl)-N´-isopropylguanidine

A solution of 3,5-dibromothiophene-2-sulfonyl chloride (5.0 g, 14.7 mmol) in toluene (30 ml) was added dropwise to a stirred mixture of isopropylguanidine p-toluene sulfonate (4.0 g, 14.7 mmol) in 35 ml of 1 N sodium hydroxide and 30 ml of toluene. The mixture was stirred at room temperature for 30 min and the crude product was isolated as an yellow oil by extraction with dichloromethane. The oil was crystallised by trituration with ethyl acetate/heptane to give 1.87g (32 %) of the title compound; mp 146-148° C.

b) 6-Bromo-3-isopropylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

A mixture of N-(3,5-dibromo-2-thienosulfonyl)-N´-isopropylguanidine(1.0 g, 2.5 mmol), potassium carbonate (0.44 g, 3.2 mmol) and copper bronze (40 mg) in dry *N,N*-dimethylformamide (10 ml) was stirred at 150° C for 1 h under nitrogen. To the cooled mixture was added 20 ml of water and the mixture was treated with decolorising charcoal and filtered. The filtrate was evaporated to dryness and the residue was treated with 5 ml of water and 4 M hydrochloric acid to pH < 2. The solid was isolated by filtration, washed with

water and dried to give 0.48 g (59 %) of the title compound ; mp 279-281° C; ^{1}H-NMR (DMSO-d_6): δ d 1.16 (d, 6H), 3.86 (m, 1H), 7.14 (s, 1H), 7.18 (br, 1H), 10.74 (s, 1H).

EXAMPLE 17

6-Chloro-3-methylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

a) N-(2,5-Dichloro-3-thienylsulfonyl)-S-methylisothiourea

2,6-Dichlorothiophene-3-sulfonyl chloride (5.0 g, 19.8 mmol) was gradually added to a stirred mixture of S-methylisothiourea sulfate (5.5 g, 19.8 mmol) in 40 ml of 1 N sodium hydroxide and 50 ml of ether. The mixture was stirred at room temperature for 20 h and the ether phase was evaporated in vacuo to give the product as an oil which slowly solidified. ^{1}H-NMR (DMSO-d_6): δ 2.36 (s, 3H), 7.40 (s, 1H), 8.20 (br s, 1H), 8.95 (br s, 1H). The crude product was used in the next step without further purification.

b) 6-Chloro-3-methylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

A mixture of N-(2,5-dichloro-3-thienylsulfonyl)-S-methylisothiourea (5.50 g, 18.0 mmol), potassium carbonate (2.48 g, 18.0 mmol) and copper bronze (100 mg) in dry *N,N*-dimethylformamide (30 ml) was stirred at 150° C for 2 h under nitrogen. To the cooled mixture was added 50 ml of water and the mixture was treated with decolorising charcoal and filtered. The filtrate was evaporated to dryness and the residue was treated with 25 ml of water and 4 M hydrochloric acid to pH < 2. The solid was isolated by filtration, washed with water and ether to give 2.18 g (45 %) of the title compound ; mp 324-326° C; ^{1}H-NMR (DMSO-d_6): δ d 2.50 (s, 3H), 7.44 (s, 1H).

EXAMPLE 18

6-Chloro-3-methylsulfinyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

To a suspension of 6-chloro-3-methylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide (0.35 g, 1.3 mmol) in 25 ml of acetic acid was added 1,2 ml of 35% hydrogen peroxide and the mixture was stirred at room temperature for 24 h. Water (75 ml) was added to the solution which was extracted with dichloromethane (50ml) to give 170 mg (46 %) of the title compound as white crystals; ^{1}H-NMR (DMSO-d_6): δ 2.93 (s, 3H), 7.46 (s,1H).

EXAMPLE 19

6-Chloro-3-isopropylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

N-(3-Bromo-5-chlorothienylsulphonyl)-*N*-isopropylurea (10 g, 27.7 mmol) was added to xylene (230 ml) under an atmosphere of nitrogen. Copper(I) oxide (74 mg, 0.52 mmol), caesium carbonate (13.5 g, 41.5 mmol) and water (2.3 ml) was added and the reaction mixture was heated to 120-125 °C for 12-14 h. after cooling to room temperature methanol (60 ml) was added and the reaction mixture was filtered. The crystal mass was washed with methanol (10 ml × 2) and water (230 ml) was added to the solvent mixture. The two phases were separated and the xylene phase was washed with a mixture of water and methanol (2:1; 35 ml × 2). Methanol was evaporated *in vacuum* from the aqueous/methanol phase and hydrochloric acid (1M; about 35 ml) was added to pH 1-2 under vigorous stirring. The precipitated crude product was isolated by filtration, washed with hydrochloric acid (5 ml × 2) and recrystallised from acetic acid (100 %, 29 ml) to give the title product (4.0 g, 52 %).

EXAMPLE 20

6-Chloro-3-isopropylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

N-(3-Bromo-5-chlorothienylsulphonyl)-*N*-isopropylurea (100 mg) was added to a glass screw cap vessel together with copper(II) chloride (2.2 mg), caesium carbonate (136 mg), xylene

(5 ml) and water (20 µl). The vessel was sealed and heated to 115 °C. After 21 hours the amount of product formed was 81 % (The data are found as described in example 9).

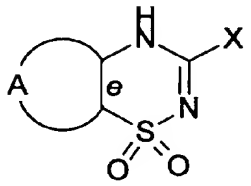
EXAMPLE 21

6-Chloro-3-isopropylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

N-(3-Bromo-5-chlorothienylsulphonyl)-*N*-isopropylurea (100 mg) was added to a glass screw cap vessel together with copper(I) oxide (2.3 mg), caesium carbonate (136 mg), n-butanol (5 ml) and water (20 µl). The vessel was sealed and heated to 115 °C. After 21 hours the amount of product formed was about 100 % (The data are found as described in example 9).

CLAIMS

1. A process for the preparation of a compound of formula I



(I)

wherein X is NR^2R^3, SR^1, $S(=O)R^1$, $S(=O)_2R^1$ or OR^1, wherein R^1 is hydrogen, C_{3-6}-cycloalkyl or (C_{3-6}-cycloalkyl)C_{1-6}-alkyl the C_{3-6}-cycloalkyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms, optionally being mono- or polysubstituted with halogen, cyano, trifluoromethyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, aryl, arylalkyl, hydroxy, oxo, nitro, amino, C_{1-6}-monoalkyl or dialkylamino; or straight or branched C_{1-18}-alkyl, C_{2-18}-alkenyl or C_{2-18}-alkynyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{3-6}-cycloalkyl, nitro, amino, C_{1-6}- monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C_{1-6}-alkoxycarbonyl, carbamoyl, formylamino, C_{1-6}-alkylcarbonylamino, aryl, aryloxy, arylalkoxy; bicycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, aryloxy, arylalkoxy, nitro, amino, C_{1-6}-monoalkyl- or dialkylamino, cyano, oxo, acyl or C_{1-6}-alkoxycarbonyl;

R^2 is hydrogen; hydroxy; C_{1-6}-alkoxy; or C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{2-6}- alkenyl or C_{2-6}-alkynyl optionally mono- or polysubstituted with halogen;

R^3 is hydrogen, C_{3-6}-cycloalkyl or (C_{3-6}-cycloalkyl)C_{1-6}-alkyl, the C_{3-6}-cycloalkyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms; or straight or branched C_{1-18}-alkyl optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{3-6}-cycloalkyl, aryl, aryloxy, arylalkoxy, nitro, amino, C_{1-6}-

monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C_{1-6}-alkoxycarbonyl, or carbamoyl;

or R^3 is $-OR^4$; $-C(=Z)R^4$; $-NR^4R^5$; bicycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, aryloxy, arylalkoxy, nitro, amino, C_{1-6}-monoalkyl- or dialkylamino, cyano, oxo, acyl or C_{1-6}-alkoxycarbonyl;

wherein R^4 is hydrogen; C_{3-6}-cycloalkyl or (C_{3-6}-cycloalkyl)C_{1-6}-alkyl, the C_{3-6}-cycloalkyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms; or straight or branched C_{1-18}-alkyl optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{3-6}-cycloalkyl, aryl, aryloxy, arylalkoxy, nitro, amino, C_{1-6}-monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C_{1-6}-alkoxycarbonyl, or carbamoyl;

Z is O or S;

R^5 is hydrogen; C_{1-6}-alkyl; C_{2-6}-alkenyl; C_{3-6}-cycloalkyl optionally mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy;
or, when or R^3 is $-NR^4R^5$, R^4 and R^5 together with the nitrogen atom form a 3-12 membered mono- or bicyclic system, in which one or more of the carbon atoms may be exchanged with nitrogen, oxygen or sulfur, each of these ring systems optionally being mono- or polysubstituted with halogen, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, nitro, amino, cyano, trifluoromethyl, C_{1-6}-monoalkyl- or dialkylamino, oxo;

or, when X is $-NR^2R^3$, R^2 and R^3 together with the nitrogen atom form a 3-12 membered mono- or bicyclic system, in which one or more of the carbon atoms may be exchanged with nitrogen, oxygen or sulfur, each of these ring systems optionally being mono- or polysubstituted with halogen, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, nitro, amino, cyano, trifluoromethyl, C_{1-6}-monoalkyl- or dialkylamino or oxo;

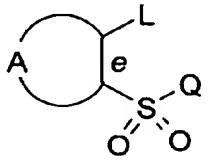
A together with the carbon atoms forming bond *e* of formula I represents a 5 membered heterocyclic system comprising one or more nitrogen-, oxygen- or sulfur atoms, the heterocyclic system optionally being mono- or polysubstituted with halogen; C_{1-18}-alkyl; C_{3-6}-

cycloalkyl; hydroxy; C_{1-6}-alkoxy; C_{1-6}-alkoxy-C_{1-6}-alkyl; nitro; amino; cyano; cyanomethyl; perhalomethyl; C_{1-6}-monoalkyl- or dialkylamino; sulfamoyl; C_{1-6}-alkylthio; C_{1-6}-alkylsulfonyl; C_{1-6}-alkylsulfinyl; C_{1-6}-alkylcarbonylamino; arylthio, arylsulfinyl, arylsulfonyl, aryl, arylalkyl, aryloxy, the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, perhalomethyl, halogen, hydroxy or C_{1-6}-alkoxy; C_{1-6}-alkoxycarbonyl; C_{1-6}-alkoxycarbonyl-C_{1-6}-alkyl; carbamyl; carbamylmethyl; C_{1-6}-monoalkyl- or dialkylaminocarbonyl; C_{1-6}-monoalkyl- or dialkylaminothiocarbonyl; ureido; C_{1-6}-monoalkyl- or dialkylaminocarbonylamino, thiocarbamyl; thioureido; C_{1-6}-monoalkyl- or dialkylaminothiocarbonyl- amino; C_{1-6}-monoalkyl- or dialkylaminosulfonyl; carboxy; carboxy-C_{1-6}-alkyl; acyl; formyl; or a 5 - 6 membered nitrogen, oxygen or sulfur containing ring, optionally substituted with C_{1-6}-alkyl or phenyl, the phenyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, perhalomethyl, halogen, hydroxy or C_{1-6}-alkoxy;

or a salt thereof with a pharmaceutically acceptable acid or base, or an optical isomer thereof, or a tautomeric form thereof, or metabolites or prodrugs thereof

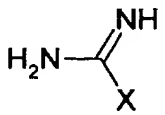
comprising one of the following methods:

a) reacting a compound of formula II



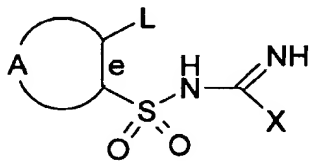
(II)

wherein A is as defined above, L is a leaving group selected from alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro or halogen and Q is halogen with a compound of formula III,



(III)

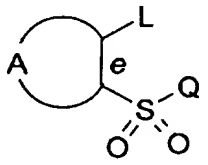
wherein X is NR^2R^3, wherein R^2 and R^3 are defined above, or a suitable salt th reof, in the presence of a suitable base in solvent 1 to form a compound of formula IV



(IV)

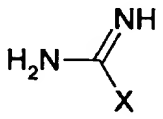
wherein A, L and X are as defined above, and thereupon cyclization of a compound of formula IV by treatment without or with a metal catalyst in solvent 2 in the presence of a base to form a compound of formula I, or

b) reacting a compound of formula II



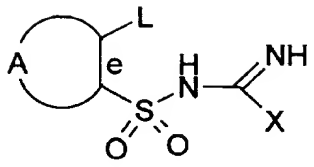
(II)

wherein A is as defined above, L is a leaving group selected from alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl or halogen and Q is halogen with a compound of formula III,



(III)

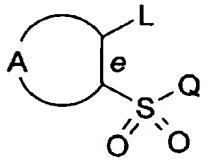
wherein X is SR^1, $S(=O)R^1$ or $S(=O)_2R^1$, wherein R^1 is defined above, or a suitable salt thereof, in the presence of a suitable base in solvent 1 to form a compound of formula IV



(IV)

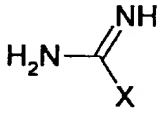
wherein A, L and X are as defined above, and thereupon cyclization of a compound of formula IV by treatment with or without a metal catalyst in solvent 2 in the presence of a base to form a compound of formula I, or

c) reacting a compound of formula II



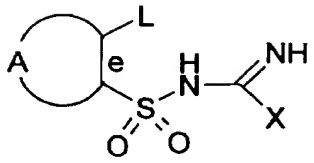
(II)

wherein A is as defined above, L is a leaving group selected from alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl or halogen and Q is halogen with a compound of formula III,



(III)

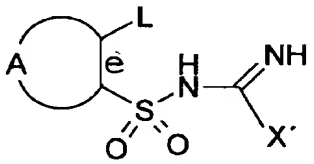
wherein X is OR^1, wherein R^1 is defined above, or a suitable salt thereof, in the presence of a suitable base in solvent 1 to form a compound of formula IV



(IV)

wherein A, L and X are as defined above, and thereupon cyclization of a compound of formula IV by treatment with or without a metal catalyst in solvent 2 in the presence of a base to form a compound of formula I, or

d) transforming a compound of formula IV to a compound of formula IV'



(IV')

wherein A and L are as defined above and X' is transformed into X and X' ≠ X, and cyclization of a compound of formula IV' by treatment with or without a metal catalyst in solvent 2 in the presence of a base to form a compound of formula I, or

e) transforming a compound of formula I, prepared as described above, by oxidation or substitution or both, to form another compound of formula I.

2. A compound selected from the group consisting of:

3-Amino-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
7-Bromo-6-chloro-3-propylaminothieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-Bromo-3-(*sec*-butylamino)-6-chloro-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-Bromo-6-chloro-3-cyclobutylamino-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-methylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-methylsulfinyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

obtained by a process according to claim 1.

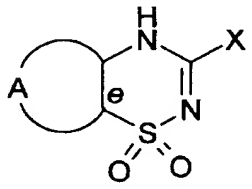
3. A pharmaceutical composition for the treatment or prophylaxis of Type I or Type II diabetes comprising a compound according to claim 2 and a pharmaceutically acceptable carrier.

4. The use of a compound according to claim 2 to manufacture a medicament in solid or liquid form for the treatment of Type I or Type II diabetes.

5. A method of treating Type I or Type II diabetes which comprises administering an effective or prophylactic amount of a compound according to claim 2 to a person suffering from Type I or Type II diabetes.

ABSTRACT

The present invention relates to a novel processes for preparing pharmaceutically active compounds of formula I:



(I)

wherein A and X are defined in the description and intermediates therefor.